Vascular endothelial growth factor in serum and in the follicular fluid of patients undergoing hormonal stimulation for in-vitro fertilization

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A cross-sectional study regarding endocrine and cytokine parameters in human follicular fluid (FF) as compared to serum values following hormonal stimulation for in-vitro fertilization was conducted. The patients (n = 32) were treated sequentially with the luteinizing hormone-releasing hormone (LHRH) agonist buserelin followed by a combination of buserelin plus highly purified follicle stimulating hormone and finally human choric gonadotrophin, in order to induce ovulation. The FF content of pro-inflammatory (IL-1, IL-6), and anti-inflammatory (IL-1ra, IL-10) cytokines, of the immune response-related soluble interleukin-2 receptor (sIL-2R), as well as the mitogens vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) were determined. Routine evaluation included peripheral blood cell counts, morphological data of the ovary and ova, ovarian steroids, prolactin concentrations and thyroid function parameters [free thyroxine (fT4), thyroglobulin]. The concentrations of IL-6, IL1-ra, sIL-2R, VEGF and bFGF in the FF compartment were higher than in serum in the majority of cases. Regression analysis showed a significant association between the serum and FF concentrations of fT4 (P = 0.04; y = 0.37 + 0.34x) and IL-6 (P = 0.002; y = 0.78 + 0.5x). Multiple regression analysis revealed that progesterone played a role in determining VEGF concentrations in the FF (P = 0.07; y = 0.37 + 0.86x). Thyroglobulin concentrations within the FF were extremely low, whereas fT4 concentrations in the FF were similar to those in serum. Patients with a previously diagnosed hypothyroidism tended to have lower serum oestradiol and higher serum progesterone when compared to euthyroids. We conclude that the human FF represents a functional compartment that integrates endocrine, immunological, and mitogenic signalling that is unique for each ovarian follicle. The close association between progesterone and VEGF within the FF suggests a close association of this mitogen to gonadotrophin stimulation, confirming the ovary as a production site of VEGF.

Key words: cytokines/IVF/mitogens/steroids/thyroid hormones/VEGF

Introduction

The endocrine aspects of the regulation of ovarian follicular function have received considerable attention in past years due to their immediate relevance for therapeutic measures in the field of human reproduction. Recent interest has recently focused on the possible interaction of cytokines and mitogens within the ovary (Adashi, 1992; Moncayo and Moncayo, 1995a, b; Elchalal and Schenker, 1997). Vascular endothelial growth factor (VEGF), a mitogen related to increased angiogenesis (Dissen et al., 1994), and which is responsive to gonadotrophin stimulation (Neulen et al., 1995), has been described recently in the follicular fluid (FF)(Lee et al., 1997a). VEGF has been postulated to be a mediator of the so-called ovarian hyperstimulation syndrome (OHSS) (Elchalal and Schenker, 1997; Rzik et al., 1997). Besides the gonadotrophin-dependent production of VEGF, interleukin 6 (IL-6) appears to induce the expression of VEGF in vitro (Cohen et al., 1996). In turn VEGF can activate mitogen-activated protein kinase (MAPK), an action which can be blocked by an N-terminal 16 kDa fragment of human prolactin (D’Angelo et al., 1995). These data suggest that both endocrine as well as cytokine interactions are potentially involved in the regulation of VEGF production. As a consequence, the aim of this study was to consider these two functional limbs, i.e. both endocrine and cytokine, in relation to VEGF production after hormonal stimulation for in-vitro fertilization. Endocrine parameters included thyroid function, prolactin, cortisol and sex steroids. Cytokine parameters included the pro-inflammatory interleukin-1 (IL-1), and interleukin-6 (IL-6), as well as the anti-inflammatory interleukin-10 (IL-10), and the interleukin-1 receptor antagonist (IL-1ra), and finally the antigen related soluble interleukin-2 receptor (sIL-2R).

Materials and methods

Patients and IVF stimulation procedure

We studied a series of 32 consecutive patients participating in the in-vitro fertilization (IVF) programme of the Endocrine Unit, Department of Obstetrics and Gynecology, University of Innsbruck. The mean (±SD) age was 32 ± 4 years (range 25–38). Twenty five patients were studied only during one stimulation cycle, whereas five patients were studied more than once (four cases twice, one case three times). All patients underwent a standard stimulation protocol. This included: (i) down-regulation with a luteinizing hormone-releasing hormone (LHRH) agonist containing buserelin acetate in a nasal application form (0.9 mg t.i.d., Suprecur®; Hoechst, Frankfurt, Germany) beginning on the 21st day of the previous menstrual cycle. LHRH agonist application was continued through the next stimulation cycle until follicle rupture was induced. The total number of LHRH treatment
days was recorded for each patient; (ii) on the 5th day after menstruation s.c. application of highly purified follicle stimulating hormone (FSH HP; Serono, Freiburg, Germany) was started at an initial dose of 3 vials/day (225 IU FSH/day). The dose was adjusted in the following days according to the clinical response and the size of the ovarian follicles by means of ultrasound (mean 2 vials/day); (iii) when a follicular diameter of 20 mm was achieved, 10 000 U of human chorionic gonadotrophin (HCG) were given i.m. in order to achieve follicular rupture. At 34–36 h after HCG administration the ovarian follicles were punctured in order to collect and pool all of the follicular fluid. Only clear aspirates were included, whereas blood contaminated samples were not. Parallel to this intervention, a sample of peripheral blood was taken. In two additional patients, selected randomly, individual samples of each follicle (n = 9) were collected separately. At the time the follicular puncture was done, both blood and follicular fluid samples were obtained and centrifuged immediately. The supernatant was stored frozen at –20°C. The results of the stimulation procedure were evaluated according to the number of oocytes, the quality of retrieved oocytes, the number of fertilized ova, and pregnancy.

**Endocrine evaluations**

Prior to starting hormonal treatment for IVF thyroid function, prolactin (PRL) concentrations and serum cortisol were determined. In cases of hypothyroidism, thyroxine was given therapeutically. At the time the follicular fluid was gained, free thyroxine (fT4) and thyroglobulin (TG) concentrations were determined both in serum as well as in the FF. Progesterone and oestradiol concentrations were also determined in both compartments, whereas cortisol concentrations were only measured in the FF samples. All determinations were done using commercially available radioimmunoassay methods. At the time the puncture was done, blood count parameters (WBC and platelet counts) were also determined.

**Cytokines and mitogens**

The determination of interleukin-1 (IL-1; R&D Systems, Minneapolis, MN), interleukin-10 (IL-10; BioSource International, Camarillo, CA, USA), the interleukin 1-receptor antagonist (IL1-ra; R&D Systems, Minneapolis, MN, USA), interleukin-6 (IL-6; Medgenix, Fleursus, Belgium), and of the soluble form of the interleukin-2 receptor (sIL-2R; Immunotec, Marseille, France) were carried out using ELISA systems. The mitogenic substances VEGF and basic fibroblast growth factor (bFGF) were determined using commercially available ELISA systems (Quantikine; R&D Systems).

**Data analysis of FF and serum concentrations**

The serum and FF concentrations of the investigated parameters were compared by means of regression analysis. In order to determine the best predictor of VEGF concentrations within the FF, multiple regression analysis was done. Discrete variables were analysed using contingency tables. All evaluations were done using the SPSS statistical software, including procedures for descriptive statistics. For details on statistical methods refer to Munro and Page (1993).

**Results**

**LHRH and FSH dose requirement**

During the initial phase of ovarian desensitization using buserelin (LHRH-1), the mean (±SD) duration of therapy until menses occurred was 14.7 ± 7.4 days (range 6–37). LHRH treatment followed for a mean of 10.3 ± 3.2 days (range 6–19) (LHRH-2) before HCG was administered. The mean total duration of LHRH treatment (LHRH-1 + LHRH-2) was therefore 24.9 ± 8.8 days (range 12–50). The mean number of FSH HP vials required for follicle maturation was 22 ± 5 (range 14–34). Neither drug dose requirement showed any association with the age of the patients.

**Comparison of serum and FF concentrations**

Of all parameters studied, TG showed the lowest values in the FF as compared to the serum values reaching a maximum of 1.7%. In 95% of all samples the concentrations of IL-1 and IL-10 were close to the lower detection limit of the systems. As a consequence these results are not presented in any further detail. All other values are presented in Table I, including the results of regression analysis. The majority of parameters, with the exception of fT4 and IL-6, showed no significant association.

**Haematological values and study parameters**

The peripheral white blood cell count was unrelated to any of the inflammatory or mitogenic parameters studied.

**Thyroid function**

Thyroglobulin concentrations within the FF were extremely low whereas fT4 concentrations were similar in FF and serum. This selective passage of low molecular weight substances (fT4 versus TG) into the FF could suggest a process of passive diffusion. The concentrations of fT4 in serum remained constant both before and after hormonal stimulation treatment. Patients who had initially had a hypothyroid function 2–3 months before stimulation (‘hypothyroids’, n = 3), and who were now on thyroxine substitution, showed no difference in their mean concentrations of PRL as compared to those who had a normal thyroid function (20.3 ± 1.3 versus 13.9 ± 7.9 ng/ml). A similar situation was also observed for progesterone (hypothyroids: 7.8 ± 6.9; euthyroids: 4.6 ± 3.7 ng/ml) whereas an opposite trend was observed for oestradiol (hypothyroids: 393 ± 236; euthyroids: 489 ± 343 pg/ml) and for sIL-2R (hypothyroids: 1.6 ± 1.0; euthyroids: 2.5 ± 1.5 ng/ml). The previously (i.e. pre-stimulation) documented concentrations of fT4 were closely associated to the serum concentrations of fT4 (P = 0.03; y = 0.13 ± 0.37x). In addition the actual FF–fT4 concentrations showed a significant association to those of FF progesterone (P = 0.01).

The concentration of fT4 in the FF was closely associated to the number of days of LHRH treatment in combination with FSH HP (χ² test, P < 0.01). More importantly, the duration of LHRH treatment after the initial down-regulation (termed LHRH-2 + FSH HP) was significantly associated with the pre-stimulation concentrations of PRL (χ² test, P < 0.01), i.e. a higher dose requirement was present when PRL concentrations were higher.

**Cortisol and steroid hormones**

Cortisol and the pro-inflammatory cytokines (IL-1, IL-6) as well as the anti-inflammatory ones (IL-10, IL-1ra) were not found to be associated within the local compartment. On the other hand, cortisol and progesterone in FF were significantly
Table I. Geometrical means and ranges of concentrations of the measured parameters both in serum and follicular fluid (FF). The last column shows the probability values derived from regression analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Serum (upper normal limit in serum)</th>
<th>FF</th>
<th>Regression analysis serum/FF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>geometric mean</td>
<td>minimum</td>
<td>maximum</td>
</tr>
<tr>
<td>Thyroglobulin ng/ml (70)</td>
<td>12.4</td>
<td>2.9</td>
<td>27.2</td>
</tr>
<tr>
<td>Free thyroxine pmol/l (23.4)</td>
<td>16.9</td>
<td>14.3</td>
<td>20.8</td>
</tr>
<tr>
<td>sIL-2R ng/ml (4.8)</td>
<td>2.4</td>
<td>1.2</td>
<td>7.2</td>
</tr>
<tr>
<td>IL-6 pg/ml (5)</td>
<td>11.4</td>
<td>3.0</td>
<td>29.0</td>
</tr>
<tr>
<td>IL-1ra pg/ml (100)</td>
<td>895.7</td>
<td>364.0</td>
<td>2989.0</td>
</tr>
<tr>
<td>bFGF pg/ml (n.d.)</td>
<td>3.9</td>
<td>0.1</td>
<td>16.4</td>
</tr>
<tr>
<td>VEGF pg/ml (n.d.)</td>
<td>430.7</td>
<td>91.9</td>
<td>884.1</td>
</tr>
</tbody>
</table>

NS = not significant.

Figure 1. Progesterone (ng/ml) and VEGF (pg/ml) concentrations in the follicular fluid (P = 0.007, regression analysis y = 0.37 + 0.86x).

associated. The mean (geometrical) concentration of cortisol in the FF was 60.84 ng/ml (range 32.3–102.9).

**VEGF concentrations**

A central observation was that of significantly elevated concentrations of VEGF within the FF, while serum concentrations of VEGF were unrelated to those in FF. Multiple regression analysis revealed that only progesterone had a significant association with FF VEGF (P = 0.007; y = 0.37 + 0.86x) Figure 1). The concentrations of VEGF and bFGF were not related.

**Interleukin-1 receptor antagonist**

The concentration of IL-1ra in serum or FF was not correlated with the number of follicles observed, nor with the number of ova recovered, nor with the quality of either the ova or the embryos. Furthermore this parameter did not show any relationship to steroid hormone concentrations (oestradiol, progesterone).

**Analysis of individual FF samples**

Table II shows the results for individual FF samples observed in two patients. It can be clearly seen that each FF was different regarding any of the measured parameters.

![Figure 2](image)

**Figure 2.** Theoretical model depicting endocrine, cytokine, and mitogenic signalling in the follicular fluid (solid lines denote stimulation; broken lines, inhibition). Gonadotrophin stimulation will induce a rise in the concentration of steroids [oestradiol (E2), progesterone] as well as of vascular endothelial growth factor (VEGF). VEGF [and interleukin (IL)-6?] induces hypervascularization and permeability. This induces diffusion of cortisol and free thyroxine (fT4) into the follicular fluid, also improving oxygenation. The prevailing thyroid function influences the concentrations of prolactin. Prolactin can act as an antagonist of VEGF activity, as well as a modulator of the hypothalamic integration of luteinizing hormone-releasing hormone (LHRH) and follicle-stimulating hormone (FSH) treatment.

**Discussion**

Hormonal treatment for in-vitro fertilization is currently a common therapeutic procedure. The usual evaluation parameters of such a treatment are related mostly to oocyte number, ova quality and finally to pregnancy success. Recent experimental and clinical data have pointed out the potential relevance of both endocrine and cytokine effects on ovarian function (Moncayo and Moncayo, 1995a, b) within the context of IVF. In this study, which did not include patients who presented with OHSS, we were able to document some of these changes and we would like to centre the discussion on the finding related to the mitogenic substance VEGF in relation only to the ‘normal’ response to hormonal stimulation.

Departing from the central event of hormonal stimulation of the ovary, increased vascularization and increased permeability...
result as a response to HCG (Macchiarelli et al., 1991). In rat ovaries these changes have been reported to be related to the production of the mitogen VEGF (Dissen et al., 1994; McClure et al., 1994). Expanding these experimental data, we provide evidence that VEGF is produced locally in the human ovarian follicle. In addition, the analysis of two patients with nine individual FF samples each revealed the unique functionality of each follicle. Corresponding to the postulate of VEGF regulation being gonadotrophin-driven (Neulen et al., 1994), our results showed a significant association between progesterone and VEGF. In addition to this, it has been reported that the mechanisms valid for increased oxygenation concentrations within the FF also influence the concentrations of VEGF (Van Blerkom et al., 1997). Oxygen utilization and energetic processes which are physiologically modulated through thyroid hormones would then occur according to the concentration of follicular and vascular development. Studies that have demonstrated the presence of thyroid hormone receptors (Wakim et al., 1993; Zhang et al., 1997) complement our proposal that the thyroid has an influence on ovarian function (Moncayo and Moncayo, 1997).

Besides these considerations on VEGF we would like to stress the fact that cytokines which correspond to the inflammatory and antigen-dependent responses (sIL-2R, IL-1ra, IL-6) as well as bFGF are present in a higher concentration in the FF, suggesting again a local production site of these factors. It follows that both compartments, i.e. FF and serum, are functionally different. The proposed functional interactions of IL-1ra, i.e. to be an antagonist of HCG-induced ovulation in the rat (Simón et al., 1994), could not be documented in our study. Our data did not show any relation between IL-1ra and any potential target within this system (follicle number, number of ova, ova quality, embryo quality, steroid hormone production). Adashi (1992) has already expressed his concerns about extrapolating data arising from animal models. Finally, the sole determination of cortisol concentrations in FF was not associated with any predictive parameter related to pregnancy (Michael et al., 1993). As a whole it can be stated that neither the cytokines studied nor cortisol concentrations were associated with the IVF outcome.

The study of thyroid function was included by us due to its relationship to PRL concentrations since hyperprolactinaemia can occur in hypothyroidism (Fish and Mariash, 1988). The initial PRL values and the FF to serum relation for fT4 showed an association with the duration of LHRH treatment, while being administered in parallel to FSH, before HCG could be administered. Patients with a previous hypothyroidism tended towards higher concentrations of PRL, and these were also correlated to higher concentrations of progesterone (Piekos et al., 1995). On purely speculative grounds, we suggest that elevated PRL could interfere locally with VEGF actions (Clapp et al., 1993; D’Angelo et al., 1995) and that in order to overcome this handicap, the production of progesterone has to be increased. Additional hypothalamic actions of prolactin could also be expected (Clapp et al., 1994). This is reflected by the longer period of FSH administration required. On practical grounds, this finding stresses the need for proper diagnosis and treatment of overt or latent hypothyroidism.

Since the initial submission of our study a series of related publications dealing with VEGF have appeared. Antczak et al. (1997) revealed a mechanism by which granulosa cells can accumulate growth factors by means of tethered structures related to an apocrine mechanism. Lee et al. (1997b) described an in-vitro system the lack of interrelationship between progesterone and VEGF production while HCG showed a direct enhancing mechanism. Besides these functional relations, Elchalal and Schenker (1997) as well as Mathur et al. (1997) have reviewed theoretical considerations that could involve VEGF in the development of OHSS. Since our study did not include patients with this syndrome, we cannot discuss these hypotheses based on our data. However, it is certainly important to learn more about the fine regulatory mechanisms that control endocrine, metabolic, mitogenic as well as angiogenic processes in the ovary. A disruption of these fine control processes would then occur according to the concentration of follicular and vascular development.

### Table II. Analysis of nine individual follicular fluid (FF) samples in two in-vitro fertilization (IVF) patients

<table>
<thead>
<tr>
<th>Name</th>
<th>Sample type</th>
<th>Sample number</th>
<th>IL-1ra pg/ml</th>
<th>sIL-2R ng/ml</th>
<th>IL-6 pg/ml</th>
<th>VEGF pg/ml</th>
<th>Free thyroxine pmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt. H</td>
<td>Serum</td>
<td>1205</td>
<td>1.9</td>
<td>8</td>
<td>455</td>
<td>16.4</td>
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<td>FF</td>
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<td>433</td>
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<td>45</td>
<td>1227</td>
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<td>760</td>
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<tr>
<td>FF</td>
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<td>2440</td>
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<td>FF</td>
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<td>30</td>
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<td></td>
</tr>
<tr>
<td>FF</td>
<td>7</td>
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<td>33</td>
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<tr>
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<tr>
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<tr>
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</tr>
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<td>996</td>
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<td>26</td>
<td>2304</td>
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</table>

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mechanisms, e.g. the loss of ovarian endocrine function, has been shown recently to be related to the development of angiogenesis in ovarian carcinoma while persistent gonadotrophin stimulation is taking place (Schiffenbauer et al., 1997).

In conclusion, our data reveal changes related to endocrine and cytokine function within the FF during IVF (Figure 2). The pathway which we have chosen, i.e. a complex model that attempts to integrate these mechanisms, expands the information on concentration that can be obtained from simplistic ovarian models (Lee et al., 1997b). One central issue corresponds to the detection of VEGF in the FF suggesting an in-vivo role in mitogenesis and vascular permeability, while at the same time it appears to be closely related to hormonal response (progesterone production). Prolactin concentrations, together with thyroid function, appear to be potential regulators of ovarian (interference of VEGF action or expression?) and pituitary response to stimulation. Thyroxine concentrations within the FF together with corresponding oxygenation concentrations (Van Blerkom et al., 1997) would be regulating the metabolic functions, e.g. decreased function can be expected in hypothyroidism. The increased concentrations of both pro-inflammatory and anti-inflammatory cytokines suggest the participation of locally regulating cells, whereas this reaction appears not to be correlated directly with outcome.

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Received on December 2, 1997; accepted on September 3, 1998